NDA 19-436/S-012
NDA 20-343/S-008 JUL 6 1999

Sanofi Pharmaceuticals, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Dr. Torre:

Please refer to your supplemental new drug applications dated April 13, 1999, received April 15, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Primacor (milrinone lactate) Injection (NDA 19-436) and Primacor (milrinone lactate) in 5% Dextrose Injection (NDA 20-343).

We acknowledge receipt of your submissions dated April 27 and May 10, 1999.

These supplemental new drug applications provide for final printed labeling revised as follows:

The sixth paragraph under **CLINICAL PHARMACOLOGY** was deleted.

The first paragraph under **CLINICAL PHARMACOLOGY: Pharmacodynamics** was revised to read as follows:

> In patients with heart failure due to depressed myocardial function, Primacor produced a prompt dose and plasma concentration related increase in cardiac output and decreases in pulmonary capillary wedge pressure and vascular resistance, which were accompanied by mild-to-moderate increases in heart rate. Additionally, there is no increased effect on myocardial oxygen consumption. In uncontrolled studies, hemodynamic improvement during intravenous therapy with Primacor was accompanied by clinical symptomatic improvement, but the ability of Primacor to relieve symptoms has not been evaluated in controlled clinical trials. The great majority of patients experience improvements in hemodynamic function within 5 to 15 minutes of initiation of therapy.

The following sentence was deleted from the third paragraph of the **CLINICAL PHARMACOLOGY: Pharmacodynamics** subsection:

> The heart rate was generally unchanged (increases of 3.3 and 10 percent, respectively).

The following sentence was deleted from the third paragraph of **the CLINICAL PHARMACOLOGY: Pharmacodynamics** subsection:

> Patients have been maintained on infusions of Primacor for up to 5 days.

The **INDICATIONS AND USAGE** subsection was changed to read as follows:

> Primacor is indicated for the short-term intravenous treatment of patients with acute decompensated heart failure. Patients receiving Primacor should be observed closely with appropriate electrocardiographic equipment. The facility for immediate treatment of potential cardiac events, which may include life threatening ventricular arrythmias, must be available. The majority of experience with intravenous Primacor has been in patients receiving digoxin and diuretics. There is no experience in controlled trials with infusions of Primacor for periods exceeding 48 hours.

The following **WARNINGS** section was added (in bold print):

> **Whether given orally or by continuous or intermittent intravenous infusion, Primacor has not been shown to be safe or effective in the longer (greater than 48 hours) treatment of patients with heart failure. In a multicenter trial of 1088 patients with Class III and IV heart failure, long-term oral treatment with Primacor was associated with no improvement in symptoms and an increased risk of hospitalization and death. In this study, patients with Class IV symptoms appeared to be at particular risk of life-threatening cardiovascular reactions. There is no evidence that Primacor given by long term continuous or intermittent infusion does not carry a similar risk.**
>
> **The use of Primacor both intravenously and orally has been associated with increased frequency of ventricular arrhythmias, including nonsustained ventricular tachycardia. Long-term oral use has been associated with an increased risk of sudden death. Hence, patients receiving Primacor should be observed closely with the use of continuous electrocardiographic monitoring to allow the prompt detection and management of ventricular arrhythmias.**

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert of May 10, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

At the time of your next printing, please revise the Manufacturing Statement under **HOW SUPPLIED** to add the 50 mL vial to the list of products manufactured by Abbott Laboratories.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact David Roeder, Regulatory Health Project Manager, at (301) 594-5313.

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research